Argininosuccinate neurotoxicity and prevention by creatine in argininosuccinate lyase deficiency: An in vitro study in rat three-dimensional organotypic brain cell cultures

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Abstract: The urea cycle disorder (UCD) argininosuccinate lyase (ASL) deficiency, caused by a defective ASL enzyme, exhibits a wide range of phenotypes, from life-threatening neonatal hyperammonemia to asymptomatic patients, with only the biochemical marker argininosuccinic acid (ASA) elevated in body fluids. Remarkably, even without ever suffering from hyperammonemia, patients often develop severe cognitive impairment and seizures. The goal of this study was to understand the effect on the known toxic metabolite ASA and the assumed toxic metabolite guanidinosuccinic acid (GSA) on developing brain cells, and to evaluate the potential role of creatine (Cr) supplementation, as it was described protective for brain cells exposed to ammonia. We used an in vitro model, in which we exposed three-dimensional (3D) organotypic rat brain cell cultures in aggregates to different combinations of the metabolites of interest at two time points (representing two different developmental stages). After harvest and cryopreservation of the cell cultures, the samples were analyzed mainly by metabolite analysis, immunohistochemistry, and western blotting. ASA and GSA were found toxic for astrocytes and neurons. This toxicity could be reverted in vitro by Cr. As well, an antiapoptotic effect of ASA was revealed, which could contribute to the neurotoxicity in ASL deficiency. Further studies in human ASL deficiency will be required to understand the biochemical situation in the brain of affected patients, and to investigate the impact of high or low arginine doses on brain Cr availability. In addition, clinical trials to evaluate the beneficial effect of Cr supplementation in ASL deficiency would be valuable.

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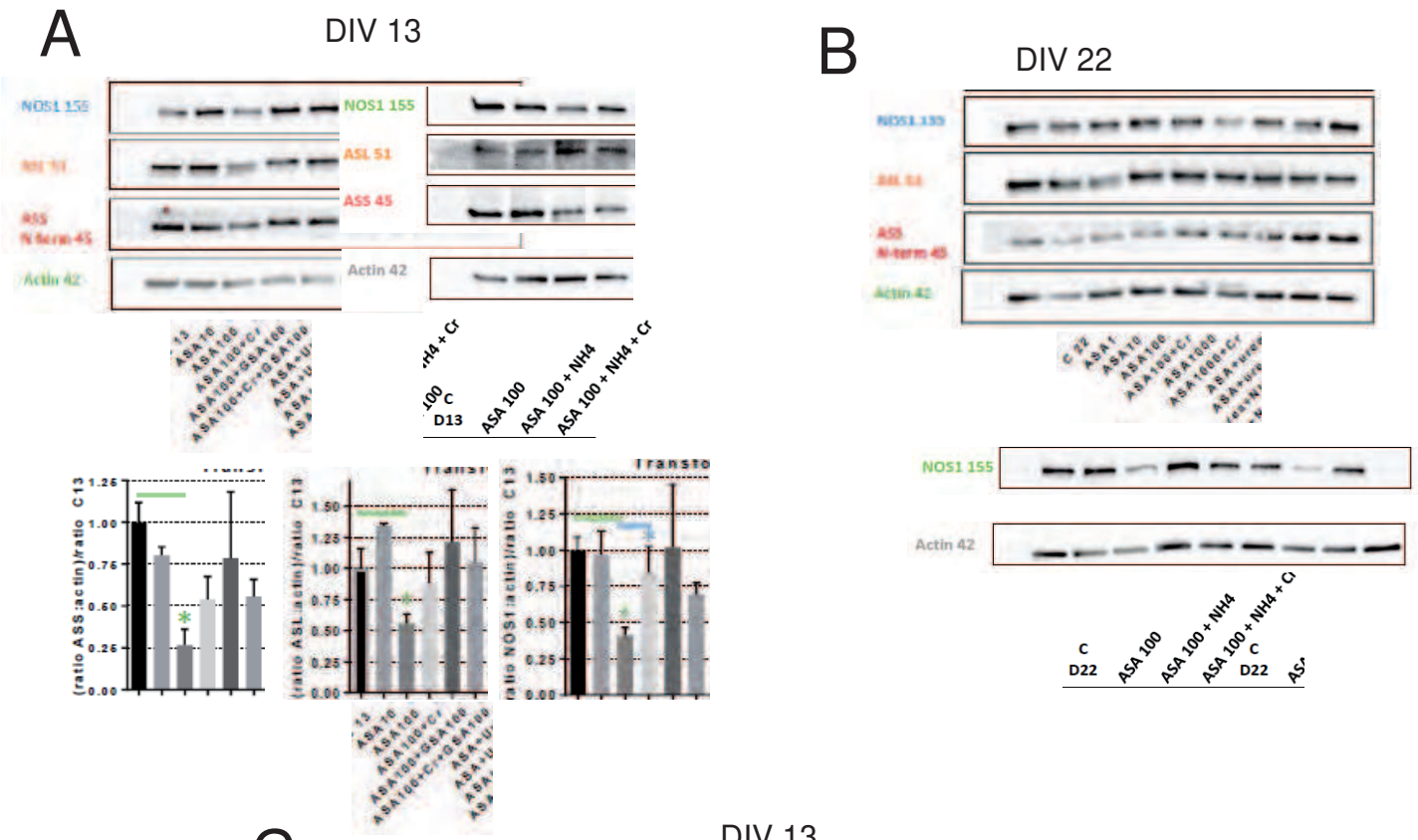

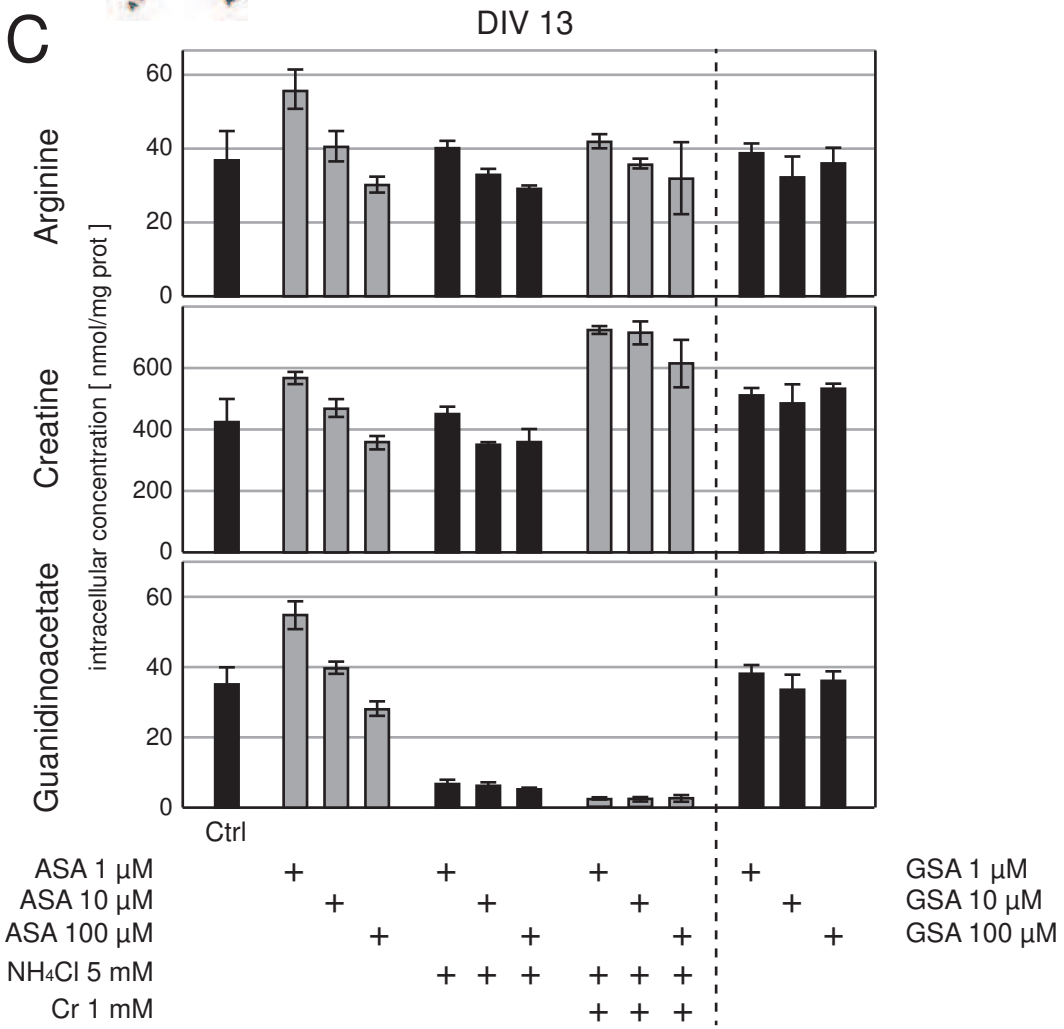

Diez-Fernandes et al, Figure NO-Arg-Cr